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METHOD AND APPARATUS FOR HIGH-PERFORMANCE SEQUENCE COMPARISON

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FIELD OF THE INVENTION

The invention relates to a method for searching multiple query sequences against one or more sequence databases. More specifically, the invention relates to a computer-implemented 10 method and apparatus that provide high-performance, high-speed, remotely accessible sequence comparison searches.

BACKGROUND OF THE INVENTION

Sequence similarity is an observable quantity that may be expressed as, for example, a 15 percentage. Comparison of newly identified sequences against known sequences often provides clues about the function of the sequences. If the sequence is a protein sequence, the sequence comparison may also provide clues as to the three-dimensional structure adopted by the protein sequence. Sequence similarity may also lead to inferences on the evolutionary relatedness, or the homology, of the sequences.

20 Current sequence databases are already immense and have continued to grow at an exponential rate. For example, the human genome project and other large scale nucleotide sequencing objectives have resulted in a large amount of sequence information available in both private and public databases. Sequence similarity searching is not simply used to compare a single sequence against the sequences in a single database, but is also used to compare or screen 25 large numbers of new sequences against multiple databases. Moreover, sequence alignment and database searches are performed tens of thousands of times per day around the world. Therefore, the ability to quickly and precisely compare new sequence data against such sequence databases is becoming more and more important.

There are many different methods for comparing sequences. Some methods, such as

those based on the analysis of transformational grammars (cf. Durbin, *et al.*, Biological Sequence Analysis, Cambridge University Press (1998), Chapter 9), compare sequences by comparing the properties of the mathematical algorithms that may be used to generate the sequences in question. However, most common methods involve the use of sequence alignment at some point 5 in the comparison process. Sequence alignment provides an explicit mapping between the residues of two or more sequences. When only two sequences are compared, the process is called pairwise alignment, but there are also methods of constructing multiple alignments that involve aligning more than two sequences.

The production of a sequence alignment result may be generically divided into two 10 separate problems. The first problem is the alignment of the query sequence with the sequences in the databases being searched. The second problem is ranking or scoring of the aligned sequences. The results of the sequence alignment search are then reported as a ranked hit list followed by a series of individual sequence alignments, plus various scores and statistics.

There are various programs and algorithms available for performing database sequence 15 similarity searching. For a basic discussion of bioinformatics and sequence similarity searching, see BIOINFORMATICS: A Practical Guide to the Analysis of Genes and Proteins, Baxevanis and Ouellette eds., Wiley-Interscience (1998) and Biological Sequence Analysis: Probabilistic Models of Proteins and Nucleic Acids, Durbin *et al.*, Cambridge University Press (1998). One of the first used algorithms for performing sequence alignment searching was incorporated into 20 the FASTA program. (Lipman and Pearson, "Rapid and sensitive protein similarity searches," Science, Vol. 227, PP. 1435-1441 (1985); Pearson and Lipman, "Improved tools for biological sequence comparison," Proc. Natl. Acad. Sci., Vol. 85, pp. 2444-2448 (1988)). The FASTA program performs optimized searches for local alignments using a substitution matrix. In order to improve the speed of the search, the program uses an observed pattern or small matches, 25 termed "word" hits, to identify potential matches before performing the more time-consuming optimization search.

A popular algorithm for sequence similarity searching is the **BLAST** (Basic Local Alignment Search Tool) algorithm, which is employed in programs such as **blastp**, **blastn**, **blastx**, **tblastn**, and **tblastx**. (Altschul *et al.*, "Local alignment statistics," Methods Enzymol.,

Vol. 266, pp. 460-480 (1996); Altschul *et al.*, "Gapped BLAST and PSI-BLAST: A new generation of protein database search programs," Nucl. Acids Res., Vol. 25, pp. 3389-3402 (1997); Karlin *et al.*, "Methods for assessing the statistical significance of molecular sequence features by using general scoring schemes," Proc. Natl. Acad. Sci., Vol. 87, pp. 2264-2268
5 (1990); Karlin *et al.*, "Applications and statistics for multiple high-scoring segments in molecular sequences," Proc. Natl. Acad. Sci., Vol. 90, pp. 5873-5877 (1993)). The approach used by the **BLAST** program is to first identify segments, with or without gaps, that are similar in a query sequence and a database sequence, then to evaluate the statistical significance of all such matches that are identified, and finally to summarize only those matches that satisfy a
10 preselected threshold of significance.

The **blastp** program compares an amino acid query sequence against a protein sequence database, while the **blastn** program compares a nucleotide query sequence against a nucleotide sequence database. The **blastx** program compares the six-frame conceptual translation products of a nucleotide query sequence (both strands) against a protein sequence database. A protein
15 query sequence is compared against a nucleotide sequence database dynamically translated in all six reading frames (both strands) by the **tblastn** program, and **tblastx** compares the six-frame translations of a nucleotide query sequence against the six-frame translations of a nucleotide sequence database. The program **blastall**, one of the implementations of **BLAST**, can be used to perform all five flavors of the **BLAST** comparison.

20 The **BLAST** program can be downloaded from the NCBI and run locally as a full executable. It can be used to run **BLAST** searches against private local databases or downloaded copies of the NCBI databases. The 1.4 and later versions of **BLAST** are capable of being run in parallel using shared memory multiprocessors. (N. Camp, "High-Throughput **BLAST**," Silicon Graphics, Inc., September 1988,
25 www.sgi.com/chembio/resources/papers/HTBlast/HT_Whitepaper.html)

Silicon Graphics, Inc. ("SGI") has developed an alternative parallel system for running multiple **BLAST** searches. (N. Camp, "High-Throughput **BLAST**," Silicon Graphics, Inc., September 1988, www.sgi.com/chembio/resources/papers/HTBlast/HT_Whitepaper.html). The system consists of a modified **BLAST** executable and a driver, and is called High-Throughput

BLAST. (“**HT BLAST**”). **HT BLAST** allows multiple sequences to be compared against multiple databases by only a single invocation of code. The output of **HT BLAST** is a summary of the High Scoring Pair information generated during the search. Through a single invocation of code, **HT BLAST** saves on startup overhead through the reuse of data structures and

5 elimination of the need to remap the databases. **HT-BLAST** also removes all parallel constructs from **BLAST**, allowing for increased single-processor speed. Parallelism has then been relocated to the driver which distributes blocks of sequences to multiple processors running **HT BLAST**. **HT BLAST** uses a dynamically scheduled loop to maintain load balance. As the independent tasks are blocks of sequences compared to multiple databases, the parallel grain-size

10 can be much greater than it is for unmodified **BLAST**. Thus, scaling to large numbers of processors is accomplished even for short sequences and small databases.

HT BLAST, however, is run on a single multiprocessor mainframe. The method and apparatus of the instant invention allows a sequence similarity searching program, such as the **BLAST** executable, to be run on multiple, networked, heterogeneous machines. Moreover, **HT-BLAST**

15 **BLAST** does not allow for dividing up collections of databases both by treating individual databases separately and by partitioning the individual databases. The method and apparatus of the instant invention do not require a shared disk architecture, whereas **HT-BLAST** assumes shared database storage and requires memory mapping. Finally, the method and apparatus of the instant invention manage multiple **BLAST** job requests through its queuing system.

20 The Blackstone Technology Group has developed a parallel processing system that allows for **BLAST** processing on a compute farm. (“SmartBlast™ – Version 1.0,” Blackstone Technology Group, <http://www.computefarm.com/compute/SmartBlast2.pdf> (2001)). Compute farms are large groups of servers that merge computing power into a single resource that is mainly used for long-running and memory-intensive applications, such as those that handle vast

25 amounts of genetic information. The system, **SmartBlast™**, distributes previously created segments of **BLAST** reference datasets to servers in the compute farm, based on demand. The segments are created using a proprietary data segmentation tool, **SmartCache™** (“SmartCache™ – Version 2.0,” Blackstone Technology Group, <http://www.computefarm.com/compute/SmartCache2.pdf>). Results are then collected, merged,

and sorted by high scoring pair and presented in a single document.

The method and apparatus of the instant invention, as noted above, may be run on a wider class of machines/operating systems, including Windows and Macintosh, whereas the

SmartBlast™ backend system only runs in a UNIX/Linux environment. In addition, in contrast

5 to the apparatus and method disclosed herein, **SmartBlast™** does not appear to divide up the input sequences. Finally, the apparatus and method of the instant invention allow for automatic partitioning of the databases during the search process, as well as in advance, based on the capabilities of the machines used for searching.

10 **SUMMARY OF THE INVENTION**

The invention relates to a computer-implemented method and apparatus for searching a plurality of query sequences against at least one sequence database containing a plurality of sequence records. The method comprises the steps of:

15 a. partitioning the plurality of query sequences into a set of smaller subsets of query sequences;

b. partitioning the at least one sequence database into a set of smaller subdatabases;

20 c. designating searching tasks to be performed by associating each of said subsets of query sequences with one or more of said subdatabases, assigning each searching task to one of a group of computers operating in parallel, wherein each member of the group of computers operating in parallel has at least one searching task assigned thereto, and executing at least some of the assigned searching tasks using the group of computers operating in parallel; and

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d. collecting search results from the executed searching tasks and generating a unified sequence search result in accordance with the collected search results.

Also disclosed is an apparatus for performing the above method, wherein the

apparatus comprises:

a. means for partitioning the plurality of query sequences into a set of smaller subsets of query sequences;

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b. means for partitioning the at least one sequence database into a set of smaller subdatabases;

c. means for designating searching tasks to be performed by associating each of said 10 subsets of query sequences with one or more of said subdatabases;

d. means for assigning each searching task to one of a group of computers operating in parallel, wherein each member of the group of computers operating in parallel has at least one searching task assigned thereto;

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e. means for executing at least some of the assigned searching tasks using the group of computers operating in parallel;

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f. means for collecting search results from the executed searching tasks; and
g. means for generating a unified sequence search result in accordance with the collected search results.

The invention also relates to the above method and apparatus, wherein the partitioning of 25 the query sequences and the partitioning of the sequence database is done by each member of the group of computers operating in parallel. In addition, the method may also be performed wherein the partitioning of the query sequences and the partitioning of the sequence database is based on the processing capacity of each member of the group of computers operating in parallel, and each member of the group of computers operating in parallel may assign to itself which

searching tasks it will perform. Each of the group of computers operating in parallel may perform one, two, or more searching tasks during the execution of the search, and each member may assign to itself another task once it finishes a searching task. The process may be reiterated, until all of the searching tasks are performed.

5 Each of the group of computers operating in parallel may be the same or different, and each of the group may have the same or different operating systems. Moreover, if one of the computers operating in parallel should fail, the correctness and/or precision of the search results will not be affected.

One or more of the sequence databases against which the query sequence is being
10 compared may be derived from the databases maintained by the National Center for Biotechnology Information (NCBI). The plurality of query sequences are searched against one or more sequence databases, and each of the sequence databases may or may not be split into a set of smaller databases. The sequence databases may be searched using any desired algorithm, such as the **BLAST** algorithm. The unified sequence search result may be a sequence alignment.
15 If the unified sequence search result is a sequence alignment, a raw score may be reported as part of the result. In addition, an e-score may also be reported as part of the search result, and the e-score may be normalized for each database searched as part of the generation of the unified search result. Moreover, the unified search result may be reported as a unified relevance ranked result list based on the normalized e-score.

20 The search results of each individual task may be collected by a single computer or by two or more computers of the group of computers operating in parallel. The unified search result may then be generated by interleaving the search results from the executed searching tasks on the basis of raw scores generated during the executed searching tasks. The method and the apparatus of the invention allow for superlinear speedup in the production of the unified search result,
25 based on total time required to execute all searching tasks and produce the unified search result, which is equal to the duration of the period starting when the entire searching task is placed on a list of searching tasks accessible to all of the one or more computers operating in parallel and ending when the unified result for the entire searching task is placed on a list of results and a signal to exit has been sent to all of the computers operating in parallel. Superlinear speedup

occurs when an increase in the number of computers operating in parallel causes a greater than *pro rata* reduction in the total time, as when the time required using four computers operating in parallel is less than one-half of the time required with two computers operating in parallel.

5 **BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 is a flow chart depicting an overview of the sequence comparison method of the invention.

Figure 2 illustrates a rectangular graphical representation of searching tasks that is used to describe the method of the invention.

10 Figure 3 is a multipart figure that provides a detailed example of the application of the method described in Figure 1.

Figure 4 is a timeline that corresponds to the example of Figure 3.

Figure 5 is a graphical representation of the task division and result merging operations for the example of Figure 3.

15 Figures 6(a) and (b) contain graphical comparisons of the performance of the sequence comparison method of the invention running on between 2 and 11 computers, with the performance of the NCBI **BLAST** program running on a single computer of the same type.

DETAILED DESCRIPTION OF THE INVENTION

I. DEFINITIONS

Virtual Shared Memory (VSM) allows applications to share objects and process data across distributed networks, such as local area networks. Commercially available programs, such as PARADISE® for the JAVA™ platform, using the VSM concept, provide one or more network “bulletin boards,” coordinate the processing of devices and components on a network, and facilitate their communication. Other programs that provide such network bulletin boards are well known in the art. A bulletin board may be used to store data or computer instructions, including descriptions of tasks to be executed or objects in a computer language such as JAVA. Any of the computers operating in parallel may access a VSM bulletin board by performing various operations, such as placing data on the bulletin board, examining data on the bulletin board, updating data on the bulletin board, or removing information from the bulletin board.

For example, in the instant method, a VSM bulletin board may be used to store descriptions of searching tasks and results of computations, such as the results of executing searching tasks. This bulletin board allows search tasks to be matched to the appropriate computer operating in parallel. Whenever one of the computers operating in parallel becomes idle, it will automatically check the bulletin board and process any appropriate searching tasks it finds there.

Sequence alignment is part of the process of comparing sequences for similarity, and may include introducing phase shifts or gaps into the query sequence or the sequences contained in the databases being searched in order to maximize the similarity between the sequences. Global alignment is the alignment of two sequences over their entire length, and local alignment is the alignment of a portion of two sequences.

The **BLAST** algorithm is a heuristic sequence similarity searching algorithm. For a given plurality of input query sequences and a given plurality of sequence databases, **BLAST** seeks to find one or more HSPs (high scoring pairs), each of which contains all or a portion of one sequence from the plurality of input sequences and all or a portion of one sequence from the plurality of sequence databases, such that the locally optimal ungapped alignment between the

two members of said HSP achieves a score at least equal to a specified integer minimum score value or an e-score lower than a specified e-score threshold. Each such HSP will be reported by **BLAST** in a list ordered from best scoring HSP to worst scoring HSP, provided the total number of such HSPs does not exceed a specified cutoff value for the maximum number of descriptions
5 and/or alignments to report. In the event that the total number of such HSPs does exceed said cutoff value, then **BLAST** truncates said list after reporting the maximum permitted number of HSPs.

For each input query sequence, **BLAST** operates by first finding one or more “words” (i.e., contiguous portions of a sequence in the plurality of databases) having length equal to a
10 defined integer W (defaulted to W = 3 in blastp), each of which has a local ungapped alignment with the input query sequence that achieves a score at least equal to a specified integer T when scored with a specified substitution matrix. Each such word is extended in both directions within the sequence that contains it in an attempt to find a locally optimal ungapped alignment between the input query sequence and said sequence having a score at least equal to the specified integer
15 minimum score value or an e-score lower than the specified e-score threshold. When such a locally optimal ungapped alignment is found, **BLAST** forms an HSP whose members are the aligned portions of the input query sequence and said sequence from the plurality of databases.

Scoring of sequence comparison results is the process of quantitatively expressing the relatedness of one of the query sequences to one of the sequences contained in the databases
20 being searched.

The raw score is the score of an alignment, or “S,” calculated as the sum of substitution and gap scores.

The bit score, or S', is derived from the raw score, S, by taking into account the statistical properties of the scoring system used. As the bit scores have been normalized with respect to the
25 scoring system, they can be used to compare alignment scores from different searches.

The e-score refers to the expectation value, which is the number of different alignments with scores equivalent or better than S that are expected to occur in a database search by chance. The lower the e-score, the more significant is the match.

The term sequence database or sequence databases means a collection or collections of

known sequences against which the query sequence is compared. The database may be a private database or publicly available. For example, publicly available sequence databases are compiled and maintained by NCBI.

The term query sequence or query sequences means a sequence or sequences to be
5 compared to the sequences contained in the databases being searched. A query sequence may be any biopolymer sequence of interest. For example, the sequence may be an amino acid sequence, a nucleic acid sequence, and the like.

A sequence in **FASTA** format begins with a single-line description, followed by lines of sequence data. The description line is distinguished from the sequence data by a greater-than
10 (">") symbol in the first column. It is recommended by NCBI that all lines of text be shorter than 80 characters in length. Query sequences in the **FASTA** format are expected to be represented in the standard IUB/IUPAC amino acid and nucleic acid codes.

A gap is a space introduced into an alignment to compensate for insertions or deletions in one sequence relative to another. The insertion of gaps causes the deduction of a fixed amount,
15 the gap score, from the alignment score, and extension of the gap to encompass additional monomers of the sequence is also penalized in the scoring of an alignment.

Substitution is the presence of a non-identical amino acid at a given position in an alignment. A conservative substitution is the substitution of an amino acid residue having similar physicochemical properties. Substitution in an alignment search affects the score through
20 the use of a substitution matrix, which contains values proportional to the probability that a given amino acid will mutate into a second amino acid, for all pairs of amino acids.

II. DESCRIPTION OF THE INVENTION

The method and apparatus of the present invention allow for high-speed, high precision
25 sequence comparison searching of one, two, three or more query sequences against one, two, three or more sequence databases. The method is implemented through the use of a group of computers operating in parallel, wherein the entire searching task to be performed is broken up into smaller searching tasks that are then processed by members of the group of computers operating in parallel, *i.e.*, the worker computers. Each of the group of computers operating in

parallel may be the same or different, and each of the group may have the same or different operating systems. In addition, if one of the computers operating in parallel should fail, the correctness and/or precision of the search results will not be affected. The method and apparatus of the present invention are independent of the searching program or algorithm used, and can be
5 used with any publicly available or private database. Moreover, the search result generated, the unified search result, is identical to a search result that would have been generated if the searching task had not been partitioned into smaller searching tasks.

Each worker computer may assign to itself which searching tasks it will perform, and the partitioning of the query sequences and the partitioning of the sequence databases to create
10 smaller searching tasks are done by each member of the group of computers operating in parallel. Such partitioning is based on, for example, the processing capability of each member of the group of computers operating in parallel, and may also be based on the total amount of processing capacity of the group of computers operating in parallel that can be used to perform the entire search task.

15 Figure 1 is a flow chart providing an overview of an example of an implementation of the method of the present invention. Based on the teachings of the instant specification, other implementations would be apparent to the ordinary artisan. The implementation depicted in Figure 1 interleaves the processes of creating smaller searching tasks, executing those tasks, and merging the results of the smaller searching tasks to create the unified result of the entire
20 searching task. A VSM bulletin board independent of the worker computers is used to store information about the ongoing searching process. For example, a list of searching tasks (the “Task List”) and a list of results of executing the searching tasks (the “Result List”) may be stored on the VSM bulletin board.

Initially, the list of searching tasks kept in the VSM bulletin board (*i.e.*, the Task List)
25 contains a single task representing the entire searching task. One or more worker computers may concurrently examine the searching tasks in the Task List. During the operation of the instant method, each worker computer of the computers operating in parallel may attempt to take (*i.e.*, copy and remove, in an atomic operation) a task from the Task List. The VSM system, such as PARADISE® for the JAVA™ platform, ensures that each task may be taken by at most one of

the worker computers that attempt to take a task. If there is an insufficient number of tasks on the Task List to permit each worker computer attempting to take a task to take at least one, then some of the worker computers attempting to take a task from the Task List may be forced to wait either until one or more additional tasks are added to the Task List, or until a signal to exit is received.

The execution of each searching task taken from the Task List creates a corresponding result that is stored in the list of search results kept in the VSM bulletin board (*i.e.*, the Result List). The entire searching task is complete when the Result List contains exactly one result that is the result for the entire searching task.

The execution of each searching task makes use of a number of parameters, such as cut-off values, that control the operation of the searching method (e.g., **BLAST**) and may affect the results that are computed. For each searching task taken from the task list, the instant method makes use of exactly the same set of parameters as would have been used for the entire searching task not using the apparatus and method of the instant invention. As described below, this enables the method to report a unified result for the entire searching task that is identical to the result that would be obtained if the apparatus and method of the instant invention were not used. As also described below, the method and apparatus of the instant invention, however, allow for superlinear speedup in generating the sequence comparison result.

- One or more worker computers may concurrently examine the results in the Result List.
- During the operation of the instant method, one or more of the worker computers operating in parallel may attempt to take (*i.e.*, copy and remove, in an atomic operation) a result from the Result List. The VSM system ensures that each result may be taken by at most one of the worker computers that attempt to take a result. If there is an insufficient number of results on the Result List to permit each worker computer attempting to take a result to take at least one, then some of the worker computers attempting to take a result from the Result List may be forced to wait either until one or more additional results are added to the Result List, or until a signal to exit is received.

Execution of a searching task requires some quantity of computational resources (e.g., memory, disk, CPU time, etc.), and upon taking a task, a worker computer estimates the quantity

of computational resources required to execute the task. This estimate is termed “RES(Task).” If RES(Task) is too large for that particular worker computer, the worker computer will divide the searching task into two smaller searching tasks and add one of them to the Task List kept in the VSM bulletin board. RES(Task) will then be recalculated for the one of the two smaller
5 searching tasks retained by the worker computer. The two smaller searching tasks that are the parts of the now-divided searching task are termed “Buddies.” Each new smaller searching task is marked as the other one’s Buddy, and the original undivided task is marked as the “Parent” of each of the two new smaller searching tasks.

Once a worker computer obtains a task for which RES(Task) is not too large, it then
10 estimates the fraction of the remaining computational effort represented by the task, termed GRAN(Task), and determines if it is too large. GRAN(Task) is too large if it exceeds a defined constant parameter times the ratio of the estimated computational power of the worker computer in question to the estimated total computational power of the aggregate of computers that the worker computer in question believes to be operating in parallel at the current time. If
15 GRAN(Task) is too large, the worker computer goes through a similar process of dividing the searching task into two smaller searching tasks and retaining one of them as is performed when RES(Task) is too large.

Once the worker computer has a searching task for which neither RES(Task) or GRAN(Task) is too large, it executes the searching task and computes the result for that
20 searching task. The searching task may be executed using any desired algorithm, such as the **BLAST** algorithm. The searching task is termed the worker computer’s “Present Task,” and the computed result is termed the worker computer’s “Present Result.”

The worker computer then performs an examination of its Present Task and Present Result to decide what to do next. First, the worker computer determines whether its Present Task
25 is the entire searching task. To do this, the worker computer looks at the VSM bulletin board to determine whether its Present Task has a Buddy Task. If its Present Task has no Buddy Task, then its Present Task is the entire searching task, and its Present Result is the final result for the entire searching task. In such a case, the worker computer adds its Present Result to the Result List kept in the VSM bulletin board, which will then contain exactly one result (*i.e.*, the result for

the entire searching task). At that point, the entire searching task is complete, and the worker computer then signals any waiting worker computers to exit.

If the worker computer's Present Task does have a Buddy Task, then the worker computer attempts to create a unified result for the Parent Task of its Present Task. The worker computer first looks at the VSM bulletin board to determine if the Buddy Task's result is READY, for example by searching for that result on the Result List kept in the VSM bulletin board. If it is not READY, the worker marks its Present Result as READY and adds it to the Result List kept in the VSM bulletin board. The worker computer then selects and executes another searching task if one is available on the Task List kept in the VSM bulletin board. If none is available, it waits either for a searching task to be added to the Task List, or for the signal to exit. Thus each of the group of computers operating in parallel may perform one, two, or more searching tasks during the operation of the instant method.

If the Buddy Task's result is READY, then it will be on the Result List kept in the VSM bulletin board. The worker computer then takes the Buddy Task's result from the Result List and merges its Present Result with the Buddy Task's result to produce a unified result for the Parent Task of its Present Task (which is also the Parent Task of the Buddy Task). The worker computer then discards information about its Present Task, the Buddy Task, its Present Result, and the Buddy Task's result. The worker computer then designates the Parent Task as its Present Task, and the Parent Task's unified result as its Present Result.

The worker computer then goes through similar examination and subsequent processing steps for its new Present Task and Present Result (which were previously known as the Parent Task and the Parent Task's unified result) as it did for its previous Present Task and previous Present Result. This examination and merging process is reiterated until either the worker computer determines that it has formed, as its then Present Result, the final result for the entire searching task, or the worker computer finds that the result of the Buddy Task of its then Present Task is not yet READY.

In the former case, the worker computer places its Present Result on the Result List kept in the VSM bulletin board, which will then contain exactly one result (*i.e.*, the final result for the entire searching task). At that point, the entire searching task is complete, and the worker

computer then signals any waiting worker computers to exit.

In the latter case, the worker computer marks its then Present Result as READY and adds it to the Result List kept in the VSM bulletin board. It then selects and executes another searching task if one is available on the Task List kept in the VSM bulletin board. If none is
5 available, it waits either for a searching task to be added to the Task List, or for a signal to exit.

Eventually, the reiteration of the task selection/execution and result merging processing will cause all of the searching tasks to be selected and executed, and all of the computed task results to be merged together to form a single, unified result for the entire searching task. Thus, the method will produce the correct result for the entire searching task.

10 Figures 2, 3, 4, and 5 demonstrate in more detail how the entire searching task is divided up into smaller searching tasks to be performed by each of the computers operating in parallel. Figure 6 contains several charts that illustrate the performance of the method of the present invention in comparison with a standard execution of NCBI **BLAST** on a single computer of the same speed as the worker computers used for the method. As is evident from the charts, a
15 substantial, superlinear speedup may be achieved using the method.

As illustrated in Figure 2, the entire searching task to be performed may be represented by a rectangle, with the horizontal representing the one or more databases against which the query sequences are to be compared, and the vertical representing the query sequences themselves. Any sequence database may be used, such as the sequence databases derived from
20 the databases maintained by the National Center for Biotechnology Information (NCBI).

The length of the rectangle's horizontal can be correlated to RES(Task), or the estimated quantity of computational resources required to execute the task. For efficient operation, it is only necessary for RES(Task) to estimate the quantity of the most important computational resources required to execute the task. For **BLAST**, RES(Task) should estimate the amount of
25 memory required to execute the task, since the memory is the most critical computational resource for **BLAST**. The memory requirement for **BLAST** is largely dependent on the size of the sequence database or portion thereof that is to be searched. Thus, one possible estimate for RES(Task) is equal to the sum of the length of the largest query sequence or portion thereof in the task plus the total length of the sequences in the database or portion thereof, all in **FASTA**

format, times 1.2.

If $\text{RES}(\text{Task})$ is too large, a vertical boundary is defined between individual databases or within a database, such as a boundary that most evenly divides the large rectangle representing the undivided searching task into two smaller rectangles. This introduction of a new vertical boundary is illustrated, for example, in Figure 3(b), where the boundary is introduced between two databases. This process may allow for rearrangement of databases along the horizontal in order to create a more even division without defining a boundary within a database, or in order to enable a worker computer to create searching tasks that use databases already stored in the memory of the worker computer in question.

The method also allows for the individual databases themselves to be split up to permit creation of searching tasks for which $\text{RES}(\text{Task})$ is not too large for a given worker computer. This is illustrated in Figure 3(d). Preferably, the databases are split at defined positions, such as in half, in quarters, etc., so that the results computed for each individual searching task may be more easily merged to provide the unified result. This is not, however, a requirement of the method.

The vertical of the rectangle in Figure 2 can be correlated to the relative duration of the task in question, where the duration of any searching task may be measured, for example, by the time in seconds required to execute the searching task with the particular query sequences and the database or portion thereof. The relative duration of the task in question is then equal to the fraction of the duration of the undivided entire searching task represented by the duration of the task in question.

The first division of the searching task using the estimate of $\text{RES}(\text{Task})$, *i.e.*, along the horizontal, splitting up the databases, is related to the quantity of computational resources, such as memory, available on the worker computer. The second division of the searching task, *i.e.*, along the vertical, by splitting up the query sequences, as illustrated in Figure 3(c), is related to the estimated relative duration of the searching task. In order to obtain the largest possible speedup, the method tries to ensure (1) that executed searching tasks are small enough, *i.e.*, of sufficiently *short* relative duration, so that there will be enough tasks to fully occupy all of the worker computers available for the entire searching task, and (2) that executed searching tasks

are large enough, *i.e.*, of sufficiently *long* duration, that the amount of overhead related to the use of parallelism (*i.e.*, the costs related to communication, access to the VSM, and task startup or shutdown on the individual worker computers) are small enough that the overall method is efficient. By ensuring these two properties, the method is able to achieve linear speedup

5 attributable to the full and efficient use of all of the worker computers available to perform the entire searching task. In practice, however, the method often achieves superlinear speedup because the divisions based on RES(Task) reduce the amount of I/O overhead, which leads to additional speedup beyond the linear speedup that would be expected normally.

In order to perform the second type of division, *i.e.*, along the vertical, by splitting up the
10 query sequences, the method makes use of an estimate of the granularity of the task. The granularity of a task relates (1) the fraction of the duration of the undivided entire searching task represented by the task at hand, to (2) the fraction of the total available computational processing capacity represented by the worker computer in question. The computational processing capacities of the computers may be estimated in various ways, for example, by estimating their
15 speeds (measured, for example, in residues or bases searched per second). The method does not require that any specific estimation technique be used.

The fraction of the duration of the undivided entire searching task represented by the task at hand can be estimated by:

$$\frac{t}{T}$$

where:

20 t is the estimated duration of the particular searching task at hand when executed on the worker computer, ignoring any effects due to limited amounts of memory.; and

T is the estimated duration of the undivided entire searching task when executed on the worker computer, ignoring any effects due to limited amounts of memory. Since the computed quantity is a ratio of durations, it does not matter what computer is used as a reference for
25 estimating the durations, since properties of the reference computer, such as its speed, will not affect the ratio.

The fraction of the total computational processing capacity represented by the worker computer in question can be estimated by:

$$\frac{p}{P}$$

where:

p is the estimated processing capacity of the worker computer in question; and

5 *P* is the estimated aggregate processing capacity of all of the worker computers believed by the worker computer in question to be available to perform the remaining incomplete searching tasks.

The granularity of the task can then be estimated by:

$$GRAN(Task) = \frac{t}{T} \left/ \frac{p}{P} \right.$$

10 In order to obtain the largest possible speedup, the method tries to ensure that GRAN(Task) satisfies:

$$c_1 > GRAN(Task) > c_2$$

where:

15 *c*₁ and *c*₂ are user defined tuning constants. For example, *c*₁ and *c*₂ may be defined as 0.5 and 0.25, respectively.

If GRAN(Task) is too large, the query sequences are divided into two parts so that the corresponding searching tasks that result have nearly equal values of GRAN(Task). If required, each individual query sequence may be divided into smaller query subsequences.

20 The method allows that if GRAN(Task) is too small, the task at hand may be increased in size. This may be done, for example, by combining the task at hand with another task on the Task List.

25 For each sequence database or portion thereof created by the task division process just described, a counter is kept in the VSM bulletin board of the number of remaining incomplete searching tasks that reference that sequence database or portion thereof. Whenever a worker

computer has an opportunity to select a new searching task, it will, if possible, “fixate” by selecting a task that searches the same database or portion thereof as its just-completed task, because that database or portion thereof is already loaded into the worker computer’s memory. This reduces I/O overhead and improves performance greatly. Initially, each worker computer

5 chooses a database or portion thereof on which to fixate using a weighted random variable so that the chance of choosing a particular database or portion thereof depends on the frequency of that database’s representation in all remaining incomplete searching tasks. Once a worker has chosen a database or portion thereof, it will only take tasks that reference that database or portion thereof, subject to the following two limitations:

10 (1) If there is no task on the Task List that references that database or portion thereof, the worker will wait idle for a short time (“ t_{idle} ”), and then, if there is still no such task on the Task List, the worker will repeat the database selection process, undoubtedly deciding to fixate on a new database or portion thereof; and

15 (2) After remaining fixated for a certain time span (the “*quantum*”) the worker will repeat the database selection process, most likely deciding to fixate on a different database or portion thereof.

The user of the method can specify the values of both t_{idle} and the *quantum*. An example of appropriate settings would be 10 seconds for t_{idle} and 30 minutes for the *quantum*.

Limitation (1) is designed to ensure that no worker computer remains idle for a long time 20 waiting for tasks referencing a particular database or portion thereof; this could happen without the limitation if all such tasks had been executed. Limitation (2) is designed to ensure that the worker computers in aggregate are spread reasonably uniformly across all incomplete searching tasks.

The final result of the method is a unified search result for the entire searching task. As 25 when using any sequence alignment algorithm, such as **BLAST**, the result is a list of the zero, one, two or more sequences (termed “hits”) from the database or databases that have the greatest similarity to the query sequence or query sequences. Typically, each hit in the list is reported along with a numerical score that corresponds to the degree of similarity between the hit and one or more of the query sequences. In that case, the list of hits may be ordered by either decreasing

value of the raw score of each hit or increasing value of the normalized e-score of each hit.

The user may define “cut-offs” to limit the number of hits included in the output for the entire searching task. For example, the user can limit the absolute number of hits or can specify threshold values on the size of the raw score or the e-score for each reported hit.

5 The method allows for various ways of computing the unified result for the entire searching task from the results for each of the smaller searching tasks created using the division processes described above. For example, all of the results for the smaller searching tasks could be collected by one of the worker computers operating in parallel, and one of the results could be designated as that worker computer’s Present Result. The worker computer in question could
10 then build the unified result for the entire searching task by reiterating a process of pairwise merging in which one of the results for the smaller searching tasks is merged with the worker computer’s Present Result. When all of the results for the smaller searching tasks have been merged with the worker computer’s Present Result, that Present Result will be the unified result for the entire searching task.

15 As noted above, Figure 1 is a flowchart depicting an example of implementing the instant method, which interleaves the processes of task division, task execution, and creation of the unified result for the entire searching task. This implementation of the creation of the unified result for the entire searching task may be more efficient than the simple implementation just described because it involves less overhead related to the use of the VSM bulletin board. The
20 detailed example of Figure 3 illustrates the sequence of task divisions and result mergings that might be achieved by the method using the implementation of Figure 1.

25 Whichever of the implementations is used to create the unified result for the entire searching task from the results of the smaller searching tasks, the computation is performed as a sequence of pairwise result merges. In each one, a new result is created by merging two existing results using a three-step process:

- (1) First, the sequence hits in the old results are interleaved in order of decreasing raw score;
- (2) Next, the e-score for each of the sequence hits is adjusted as described below; and
- (3) Last, any cut-offs used to limit the number of sequence hits reported for each

searching task are applied to limit the number of sequence hits reported in the new result.

In Step (2) of this process, it may be necessary to recalculate the e-scores to take into account the partitioning of the sequence database or databases, so that the results that are

5 reported are the same as if the entire searching task had never been broken up into smaller searching tasks. If each of the existing results corresponds to searching tasks referencing the same databases or portions thereof, then no recalculation is required, and the e-score reported for each sequence hit in the new result will be the same as the one reported in one or both of the existing results for the same sequence hit. If, however, the existing results correspond to

10 searching tasks referencing different databases or portions thereof, the e-scores must be recalculated. If the letters B and C represent two different databases, the number of letters in database B can be represented by B', and the number of letters in database C can be represented by C'. Then the e-score for each sequence hit in database B is recomputed using the following formula:

$$escore_{new} = escore_{orig} \cdot \left[\frac{B' + C'}{B'} \right]$$

15

Similarly, the e-score for each sequence hit in database C is recomputed using the following formula:

$$escore_{new} = escore_{orig} \cdot \left[\frac{B' + C'}{C'} \right]$$

20 As noted earlier, users often make use of cut-offs to limit the number of sequence hits reported by search methods such as **BLAST**. The instant method intends to produce essentially the same result (*i.e.*, exactly the same result, up to minor reorderings or variations due to

limitations of computer floating-point arithmetic) for the entire searching task as would have been reported without division into smaller searching tasks. To do this, the method must properly apply the same user-specified cut-offs.

Executing a searching task has the effect of implicitly creating an internal list of sequence hits ordered by decreasing raw score. Cut-offs limit the number of sequence hits included in the result for the searching task by discarding all but the best sequence hits from the internal list. For example, a cut-off might limit the number of hits to an absolute number of the best ones, or it might limit the hits to those with raw score exceeding some threshold or those with e-score below some threshold. In all cases, the particular set of sequence hits that survive the cut-off may depend on the relative ordering of the sequence hits in the internal list. Note that except for random reorderings or minor variations due to the limited accuracy of computer floating-point arithmetic, the internal list would be unchanged if it were ordered by increasing e-score instead of decreasing raw score.

Now consider any sequence hit that survives the application of cut-offs for the undivided entire searching task, i.e., the entire searching task as executed by the original **BLAST** method without division into smaller searching tasks. That hit is in one of the databases referenced by the entire searching task, and it must have survived the cut-offs because its achieved raw score, when compared to some one of the query sequences in the entire searching task (termed the “matching query sequence”), was sufficiently high relative to the raw scores of other hits.

The division process described above guarantees that at least one of the smaller searching tasks generated by the instant method must:

- (1) reference a subdatabase of the databases referenced in the entire searching task that contains the sequence hit in question; and
- (2) include the matching query sequence among its query sequences.

Certainly, the matching query sequence will be compared to the sequence hit in question during the execution of this particular smaller searching task. Since raw scores depend only on the particular pair of sequences compared, it is clear that the sequence hit in question will achieve a raw score for the smaller searching task that is equal to the raw score reported for the undivided entire searching task. Moreover, since the one or more subdatabases referenced by the

smaller searching task in question form, in aggregate, a subset of the databases referenced by the undivided entire searching task, the subdatabases will contain no more high quality sequence hits than the aggregation of databases referenced by the undivided entire searching task. Hence, the sequence hit in question will be no further from the beginning of the internal ordered list for the
5 smaller searching task in question than it is in the internal ordered list for the undivided entire searching task. Therefore, since the sequence hit in question survives the cut-offs in the undivided entire searching task, it must also survive the same cut-offs in the smaller searching task.

This argument demonstrates that each sequence that survives the cut-offs for the
10 undivided entire searching task also survives the cut-offs for at least one of the smaller searching tasks created by the instant method provided that the same cut-offs are applied to those tasks. In order to demonstrate that such a sequence also appears in the final result computed by the instant method, it is necessary to verify that Step (3) in the above process for result merging never eliminates the sequence.

15 Suppose that the two old results being merged contain all of the sequences meeting the cut-offs for the corresponding smaller searching tasks. By the fact that it interleaves based on raw score, it is clear that the interleaving performed in Step (1) produces a list of sequence hits in which, except for some potential random reordering of hits with equal scores, the sequence hits are in the same relative ordering (by decreasing raw score) as they are in the internal list for the
20 undivided entire searching task. The effect of applying a cut-off to the interleaved list then depends on the type of cut-off. If the cut-off limits the number of sequence hits to some absolute maximum number, then taking that absolute maximum number of sequences from the beginning of the interleaved list is guaranteed to be sufficient to permit eventual creation of the proper result for the entire searching task. At worst, later merging steps will discard some of the
25 included sequences in favor of others with higher scores.

If the cut-off limits the sequence hits based on a raw score threshold, then it is sufficient to include any sequence hit from the interleaved list that has a raw score equaling or exceeding the threshold raw score. Since each of the two old results now being merged already contains all of the sequence hits from the corresponding smaller searching task that meet the raw score

threshold criterion, it is clear that the new merged result will do so as well, and that further merges used to create the unified result for the entire searching task will pass these sequence hits on to the unified result.

If, instead, the cut-off limits the sequence hits based on an e-score threshold, then it is

5 sufficient to include any sequence hit from the interleaved list that has an e-score no greater than the threshold raw score. According to the formulae used to adjust the e-scores in Step (2), merging steps may increase, but will never reduce, the e-score for any particular sequence hit. Therefore, no sequence hit in the interleaved list that is excluded by the cut-off (because its e-score is too large) will ever achieve an e-score that is small enough to pass the cut-off test.

10 Similarly, none of the sequence hits eliminated by the cut-off in an earlier merging step could possibly meet the cut-off test at this stage of merging.

As a result of the above analysis, it appears that the instant method does, in fact, produce essentially the same result (*i.e.*, exactly the same result, up to minor reorderings or variations due to limitations of computer floating-point arithmetic) for the entire searching task as would have

15 been reported by ordinary **BLAST** without division into smaller searching tasks.

III. EXAMPLES

A. Example 1

Figure 3 provides a detailed example of the application of the method of the instant invention using the implementation of Figure 1. The computation in question entails the 5 searching of a group of query sequences against two databases using two processors (i.e., worker computers). Each of the lettered subfigures of Figure 3 (i.e., Figure 3(a) through Figure 3(q), inclusive) is a representation of the state of the computation at a particular instant in time. (Figure 4 contains timelines showing the activities of the processors between the time points that correspond to the subfigures. Figure 4 also contains lettered markings that correlate the 10 subfigures of Figure 3 to their specific points in time during the computation.)

Each subfigure of Figure 3 contains four sections reflective of the states of the searching task, the processors and the VSM bulletin board at the time point in question:

- (1) A rectangular representation similar to those of Figure 2 that represents the entire searching task as subdivided into smaller searching tasks at the time 15 point in question;
- (2) An illustration of the Task List and the Result List stored in the VSM bulletin board at the time point in question;
- (3) A textual description of the present activities of the worker computers at the time point in question; and
- (4) A caption describing the current state of the searching task(s) and the change(s) from the previous subfigure.

The Legend included in Figure 3 describes the graphical markings and the Task naming conventions used in the example. Similar markings are used in Figures 4 and 5, as well.

Figure 3 illustrates the most important operations in the method using the implementation 25 of Figure 1:

- (1) Figures 3(b) and 3(d) illustrate the division of tasks by dividing and/or rearranging one or more databases (i.e., represented as the introduction of a new vertical boundary).

(2) Figures 3(c), 3(e) and 3(k) illustrate the division of tasks by dividing the query sequences (i.e., represented as the introduction of a new horizontal boundary).

(3) Figures 3(f), 3(g) and 3(m) illustrate the result of executing a task which has a Buddy Task that is not READY.

5 (4) Figures 3(i) and 3(l) illustrate the case of performing a single merging step that leads to a unified task for which no further unification is possible until other tasks have been completed. (Such tasks are marked as READY and placed on the Result List in the VSM bulletin board.)

10 (5) Figures 3(o), 3(p), and 3(q) illustrate the case of repeated hierarchical merges that eventually lead to the final result for the entire searching task.

To complete the picture of the example of Figure 3, Figure 5 illustrates the task division and result merging operations using a binary tree representation. In Figure 5, each division of a searching task into two smaller searching tasks is represented by a single white rectangle (representing the searching task to be divided) containing two outward-pointing arrows, each of which leads to a smaller white rectangle representing one of the two smaller searching tasks. Analogously, the creation of a unified result for a Parent Task by merging the computed results of two Buddy Tasks is represented by two gray rectangles (the Buddy tasks) connected by outward-pointing arrows to a single larger gray rectangle (the Parent task). As with the other figures, Figure 5 contains lettered markings to correlate it with the subfigures of Figure 3.

20 **B. Example 2**

The example shown here provides a simple demonstration of the performance achievable with the invention. The example search task is specified as follows:

Query Sequences: 50 Expressed Sequence Tags (ESTs) totaling 18,500 DNA bases;

Databases: 3 separate databases downloaded from NCBI as follows:

NCBI Database	Sequences	DNA Bases (Approx.)
Drosophila	1,170	123 million
GSS Division of GENBANK	Approx. 1.27 million	651 million
E-coli	400	4.6 million

The benchmark example was run on a group of IBM Netfinity PCs, each containing a single 500-Megahertz Pentium III processor, 512 Kilobytes of cache memory, and 256 Megabytes of main memory. The PCs were connected on a switched 100 Megabit Ethernet network. All searches were made using the **blastn** variant of **BLAST** using the default set of **BLAST** parameters. The baseline BLAST was performed using the command:

blastall -d "ecoli.nt gss drosophila" -p blastn

which required a time of 2131.8 seconds on one computer.

The table below shows the timing results obtained with varying numbers of worker computers. The “Speedup” is calculated as the ratio between the baseline time and the time using the method with the specified number of worker computers. Since the results clearly show that the speedup using n worker computers may be greater than n , these results demonstrate the possibility of superlinear speedup with the method of the invention.

Worker Computers	Time (seconds)	Speedup
1	1011.0	2.11
2	646.0	3.30
3	393.0	5.42
4	259.5	8.22
5	218.0	9.78
6	191.7	11.12
7	171.0	12.47
8	167.3	12.74
9	161.0	13.24
10	151.0	14.12
11	130.0	16.40

The times and speedup values are plotted in Figures 6(a) and 6(b).

Although the present invention has been described in detail with reference to the example above, it is understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims. All cited
5 patents, patent applications, and publications referred to in this application are herein incorporated by reference in their entirety.